Title: Pharmaceutical cannabinoid utilization in a Canadian province: a population-based study (2004-2015)

Manuscript Classification: Original Cohort Study

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Abstract:

Background: Pharmaceutically-derived cannabinoids have appeared in practice guidelines as third-line alternatives for a variety of approved and off-label indications, despite the lack of a strong evidence to support their efficacy. The extent of utilization from a population perspective is unknown. The aim of this study is to evaluate the trends in pharmaceutical cannabinoid use in Manitoba, Canada.

Methods: This was a retrospective population-based cohort study using administrative data, held at the Manitoba Centre for Health Policy, from Apr.1, 2004 to Mar.31, 2015. We assessed the annual prevalence and incidence of pharmaceutical cannabinoids use, and the socio-demographic characteristics and medical conditions of users.

Results: We identified 5181 individuals who received at least one prescription for a pharmaceutical cannabinoid. There was a six-fold increase in the number of prevalent users between 2004 and 2015, rising from 21.5 to 134.9 users per 100,000 persons. The annual incidence increased from 12.1 to 62.2 users per 100,000 person-years ($p<0.0001$) over the study period. The mean (SD) age of new users was 50.6 (14.7) years and 58% were female. The highest use was among older adults, females, and urban area residents. Almost one-third of incident users had a diagnosis of fibromyalgia in a two-year period before their first cannabinoid prescription. General practitioners initiated 46.6% of prescriptions followed by anesthesiologists/pain specialists (25.8%).

Interpretation: The prevalence and incidence of pharmaceutical cannabinoid use has increased over time. These findings provide insight into the utilization of these agents before the expected introduction of recreational marijuana that may affect this trend.

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Introduction:

Cannabis is widely used in Canada; approximately 42.5% of Canadians aged 15 years and older have used cannabis in their lifetime and 17.7% of Canadians who used cannabis reported using it for medical purposes[1-2]. While cannabis has a long history of being used for a variety of conditions such as pain and epilepsy; there is a lack of high-level evidence to support its use.[3-5] The primary psychoactive compound of the cannabis plant is Δ9-tetrahydrocannabinol (THC), though, there are more than 70 other natural cannabinoid compounds identified. Pharmaceutically-derived prescription cannabinoids include nabilone, dronabinol and nabiximols. All three of which have been available in Canada, currently only nabilone and nabiximols are available.[6]

Now, the use of pharmaceutically-derived cannabinoids must be considered against the backdrop of the pending cannabis legalization in Canada slated for the summer of 2018, a move which has garnered critical attention regarding the potential economic, social and public health implications.[7-9] One particular concern is the blurring of recreational and medical use and the potential confusion in healthcare monitoring and management of those using it for medical purposes. In terms of pharmaco-therapeutic principles, issues of dose standardization and *consistent* administration are in favor of pharmaceutically prepared fixed dose-units as opposed to raw cannabis, especially when the clinical distinction in efficacy outcomes between the two has yet to be fully elucidated.[10-11]

Nabilone, a synthetic analog of THC, is a cannabinoid receptor agonist approved in 1982 in Canada for the treatment of chemotherapy-induced nausea and vomiting (CINV) not responding to conventional therapy. Dronabinol, an oral form of THC, was approved in 1994 for

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CINV and for anorexia associated with human immunodeficiency virus infection and acquired immune deficiency syndrome (HIV/AIDS), before its discontinuation in 2012. Nabiximols, an extract containing THC and cannabidiol (CBD), was approved in 2005 for central neuropathic pain in multiple sclerosis, and in 2007 for intractable cancer pain. These medications have also appeared in practice guidelines as third-line alternatives for a variety of off-label indications, such as fibromyalgia and arthritis.[12-15]

Several studies have discussed the potential efficacy and possible adverse effects of pharmaceutical cannabinoids; however, there is still a lack of information regarding their use in the general population.[3, 16-18] An understanding of the extent of utilization in the real-world can be achieved by drug utilization studies that rely on analyzing drug dispensations and physician claims that are prospectively collected for health system management. Characterizing the past trends of cannabinoid use enables a review of the appropriateness of their utilization and establishes baseline measurements before the legalization of recreational cannabis. Therefore, we analyzed the prevalence and incidence of pharmaceutical cannabinoid use in Manitoba, Canada. We also described the demographics and medical conditions of users.

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Methods:

Data Sources

A retrospective, population-based cohort study using administrative data from April/1/2004 to March/31/2015 was conducted using data obtained from the administrative databases within the Manitoba Population Research Data Repository located at the Manitoba Centre for Health Policy (MCHP), University of Manitoba.[19] This repository captures the encounters with the health system for > 98% of the Manitoba population that receives health care

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coverage through the provincial government department, Manitoba Health and Healthy Living (MHHL). [20]

Data can be linked across multiple datasets using scrambled personal health identification number (PHIN). Several databases were used, including the Drug Program Information Network (DPIN) database, available since 1995. DPIN, which includes the dispensation date, drug name, and medical specialty of the prescriber, captures all prescription drugs dispensed by community pharmacies to Manitoba residents. The Medical Services (physician claims) database provided service date and a diagnosis code using the International Classification of Diseases, Clinical Modification (ICD-9-CM); while the Discharge Abstract Database provided hospital admission and discharge dates and several diagnoses using ICD9/10 codes. The Manitoba Health Insurance Registry database provided the number of Manitoba residents at the beginning of each interval (one year), user's demographic information, and the dates of their health care coverage.

Study population and exposure definitions

We identified pharmaceutical cannabinoid users living in Manitoba during the 11-year study period, without age restrictions. Prescription dispensations were identified by their Anatomical Therapeutic Chemical (ATC) codes including nabilone (ATC A04AD11), dronabinol (A04AD10), nabiximols (N02BG10). The number of incident and prevalent users was assessed. Incident use was defined as first time use in the study period, with no record of a previous prescription, since the first year of available data, 1995, while prevalent use in a specific year, was defined as receiving at least one cannabinoid prescription in that year throughout the study period. Region of residence was defined as urban (Winnipeg, n=705,244

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and Brandon, n=48,859), or rural Manitoba, which includes all other population centers with <16,000 people in each.

The medical conditions of cannabinoid users were identified using algorithms, used in previous research, based on ICD codes from physician claims, hospitalizations, and/or use of prescription medications (Supplementary table 1). Medical claims and hospitalizations within two years before the first cannabinoid dispensation were used to ensure a recent diagnosis. We chose 11 medical conditions including the approved indications (multiple sclerosis, HIV/AIDs, and cancer, excluding in situ and skin cancer), and conditions reported in the literature as possible indications for cannabinoid use (glaucoma, epilepsy, rheumatoid arthritis, osteoarthritis, fibromyalgia, mood/anxiety disorders)[3]. Schizophrenia and substance abuse disorders were also investigated, as the use of cannabinoids is not recommended in these conditions. Chronic pain was also assessed and defined as a minimum of 180-day supply in at least 2 dispensations of opioids, NSAIDS or acetaminophen and its combinations, excluding psycholeptics and cold preparations, within the year preceding the first cannabinoid prescription.[21]

Last, the medical specialty of prescribers initiating these prescriptions was determined from the de-identified physician identification number reported on the prescription.

Statistical analysis

Annual prevalence rates of cannabinoid use were calculated by dividing the number of prevalent users in a year by the population count on December/31st of that calendar year. Annual incidence rates were calculated by dividing the number of first time users in a year by the population count, excluding prevalent users, in that calendar year. Then the annual incidence rates were calculated for sub-groups based on age, sex, and region of residence.

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Multivariable Poisson regression analysis, adjusted for age, sex, area of residence, and socioeconomic status (SES) was used to test for temporal trends in the incident and prevalent rates, which were calculated based on aggregate data for each strata. To account for health coverage that is less than one year, log person-years was included as an offset in the model. Age was included as a categorical variable and was categorized into ≤ 18, 19-45, 46-64, and ≥65 years. SES was categorized into 4 groups based on the Socio-Economic Factor Index (SEFI), which is an area level measure derived from Census data. The categorization was based on cut off points of one standard deviation from the mean into high, middle, middle-low and low SES. A p-value of ≤ 0.05 was considered significant. Data were analyzed using SAS software package for Windows, version 9.4 (SAS Institute, Inc., Cary, NC).

Ethics approval

This study was conducted in full compliance with the Personal Health Information Act of Manitoba and approved by the Health Research Ethics Board at the University of Manitoba and the Manitoba Health Information Privacy Committee.

Results:

Prescriptions

Between April/2004 and March/2015, 76,719 cannabinoid prescriptions were dispensed to 5181 unique individuals, 5033 of whom received their first prescription after April/1st, 2004. Nabilone comprised 96% of all cannabinoid prescriptions dispensed. One-third (32.2%) of the incident cannabinoid users received only one prescription. General practitioners were responsible for initiating 46.7% of the first prescriptions, followed by anesthesiologists/pain specialists (25.8%). Only 5.4% of prescriptions were initiated by oncologists.

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Incident cannabinoid use

Among all new users, the mean age was 50.6 (14.7) years and 58.3% were female. The annual incidence rate increased from 12.12 (95%CI: 12.06-12.19) to 62.21 (95%CI: 62.08-62.35) users per 100,000 person-years over the study period. The incidence of nabilone use increased from 10.76 (95%CI: 10.69-10.82) 2004/2005 to 61.91 (95%CI: 61.77-62.05) users per 100,000 person-years in 2014/2015. The incident use of both nabiximols and dronabinol was low and stable throughout the study period (Figure 1).

The incident use of cannabinoids by demographics of users is reported in figure 2. Between 2004 and 2015 the incidence rate increased by 242.51% for females and 141.03% for males (Figure 2.A). The incidence rate for the older adults (46-64 years) increased by 258.63%. The incident rate increased from 25.16 to 89.82, and from 25.92 to 48.43 per 100,000 person-years for those ≥ 65 years and younger adults (19-45 years), respectively. The youngest segment of the population (0–18 years) showed the lowest incidence of use (Figure 2.B). The incident use increased for residents of urban Manitoba from 24.06 to 61.23 and from 17.56 to 65.35 users per 100,000 person-years for residents of rural Manitoba (Figures 2.C).

Prevalent cannabinoid use

There was a six-fold increase in the number of individuals who used prescription cannabinoids between 2004/2005 and 2014/2015, rising from 252 (21.51 users per 100,000 persons) (95%CI: 21.41-21.61) to 1,776 (134.91 users per 100,000 persons) (95%CI: 134.71-135.11). The prevalence of nabilone use also increased from 18.01 (95%CI: 17.93-18.09) in 2004/2005 to 133.77 users per 100,000 persons (95%CI: 133.57 – 133.97) in 2014/2015. The prevalent use of both nabiximols and dronabinol was low and stable throughout the study period (Figure

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Incidence and prevalence rates standardized to the Canadian population based on statistics Canada data in 2016 are reported in supplementary figure 2.

The effect of user demographic on incident and prevalent use.

After adjusting for age, sex, area of residence, and the SES, the annual rate of prevalent and incident cannabinoid use increased by 1.15 and 1.09 per 100,000 persons, respectively. The upward trend was significant for both models. The effect of user demographics on use is reported in (Table1).

Medical conditions of incident cannabinoid users

We identified 1,775 incident cannabinoid users (35.26%) who had received a diagnosis of fibromyalgia, and 1,116 with a diagnosis of mood and anxiety disorders (22.17%). The percent of users who had a diagnosis for the approved indications: cancer, multiple sclerosis, and HIV/AIDS were 18.21%, 4.23%, 1.01%, respectively (Table 2). Moreover, 50.46% (n=2,540) of cannabinoid users were being treated for chronic pain in the year before their first cannabinoid prescription.

Interpretation:

This population-based study found an increase in the number of pharmaceutical cannabinoid users in Manitoba over an 11-year period, driven almost entirely by nabilone use. In 2009, there was a slight temporary decrease in the use of nabilone. Considering that there were no alternatives to Cesamet® (nabilone) by Valeant Pharmaceuticals International, Inc., this drop is likely explained by a recall of Cesamet® due to a mislabeling incident identified nationally by Health Canada.[22]

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The rates of use were higher for females; several factors can possibly affect this trend. Possibly because conditions like fibromyalgia, osteoarthritis, and mood/anxiety disorders are more common in women. As expected, the lowest rate of use was among the youngest age group as the use of cannabinoids in those <18 years is not recommended due to the lack of safety and efficacy data. The highest rate of use was among individuals between ages 46 to 64 followed by those ≥65 years; where conditions like multiple sclerosis and cancer are more prevalent. There was a difference in the rates of use among urban vs rural residents; although statistically significant, it was not substantial. The access and use of health care and age distribution in rural and urban areas might affect this trend, this requires further investigation. The financial barriers to meet medication costs could explain the differences in use among the different income groups.

The majority of medical conditions identified were pain-related conditions such as fibromyalgia, osteoarthritis, cancer, and multiple sclerosis (Table 2). Moreover, almost half of the incident cannabinoid users met the study definition of chronic pain. This pattern of use is consistent with a systematic review and meta-analysis wherein it was concluded that there is more evidence to support the use of cannabinoids for chronic pain than other indications.[3] Despite the caution required, we found that 8.3% of incident users received a diagnosis of substance abuse disorder; this could be due to the prescriber looking for an alternative to medical cannabis to those who have a history of substance use disorder. This could also indicate a need for prescribing guidelines in this population and require further investigation. The number of users who had a diagnosis for schizophrenia was very low as these agents are contraindicated when there is history of psychosis. The percentage of users who met the study definition for the approved indications was low. Moreover, one third of incident users only filled one prescription.

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Findings like these might question the efficacy and safety of these medications and the appropriateness of their off-label use.

Regarding the overall increase in use over time, this might be related to a general increased interest in medical marijuana, as nabilone represents an option that is easier to access and covered by the provincial drug program.[23] Furthermore, prescribers may prefer these agents over raw medical cannabis because they generally cause less euphoria than marijuana and hence are less prone to abuse, and because of their consistent, standardized dosing, which is highly variable with the natural cannabis products. [24-26]

However, it is unknown if this trend will continue after the legalization of cannabis that may affect the utilization of pharmaceutical cannabinoids, as several patients may favor purchasing cannabis over a physician visit and filling a prescription. This will be determined by the cost, age, quantity limits, and other administrative regulations associated with the legalization, which have been discussed elsewhere.[7]

Strengths and limitations:

This is an observational, population-based database study that captures nearly every encounter between Manitoba residents with a universal health care system, allowing for a complete assessment of the real-world drug utilization, without sampling errors. Moreover, Manitoba population is relatively stable, allowing us to follow individuals longitudinally over time with limited loss of follow-up. Despite the advantages of observational studies using administrative data, there are recognized limitations. These include potential misclassification of medical conditions using data intended for administrative, not clinical or research purposes;

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however, algorithms validated in other studies were used to minimize misclassifications. It is impossible to fully determine the intended indication for the use of cannabinoids, which have a number of potential uses. Thus, even when an associated condition is correctly identified, the clinical indication for cannabinoid use cannot be confirmed, especially in individuals with numerous co-occurring illnesses. This dilemma is especially difficult in chronic pain as there is no consensus on a validated definition for identifying pain patients using administrative data, despite the fact that numerous painful conditions can be identified. The inability to differentiate between pain, appetite stimulation, CINV, as the primary use of cannabinoids in cancer patients is another example of this limitation.

Conclusion:

Incident and prevalent cannabinoid use increased over the study period. Incident use was higher throughout the 11-year period among females and older adults. Pain and pain-related conditions represented the highest percent among the possible indications for cannabinoids. These findings provide insight into the utilization of these agents before policies regarding access to medical cannabis change. The expected introduction of recreational marijuana and its legal availability may affect this trend.

Acknowledgment:

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inferred. Data used in this study are from the Manitoba Population Research Data Repository housed at the Manitoba Centre for Health Policy, University of Manitoba, and were derived from data provided by Manitoba Health.

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Figure 1: Annual incidence of cannabinoid users (2004/05-2014/15).

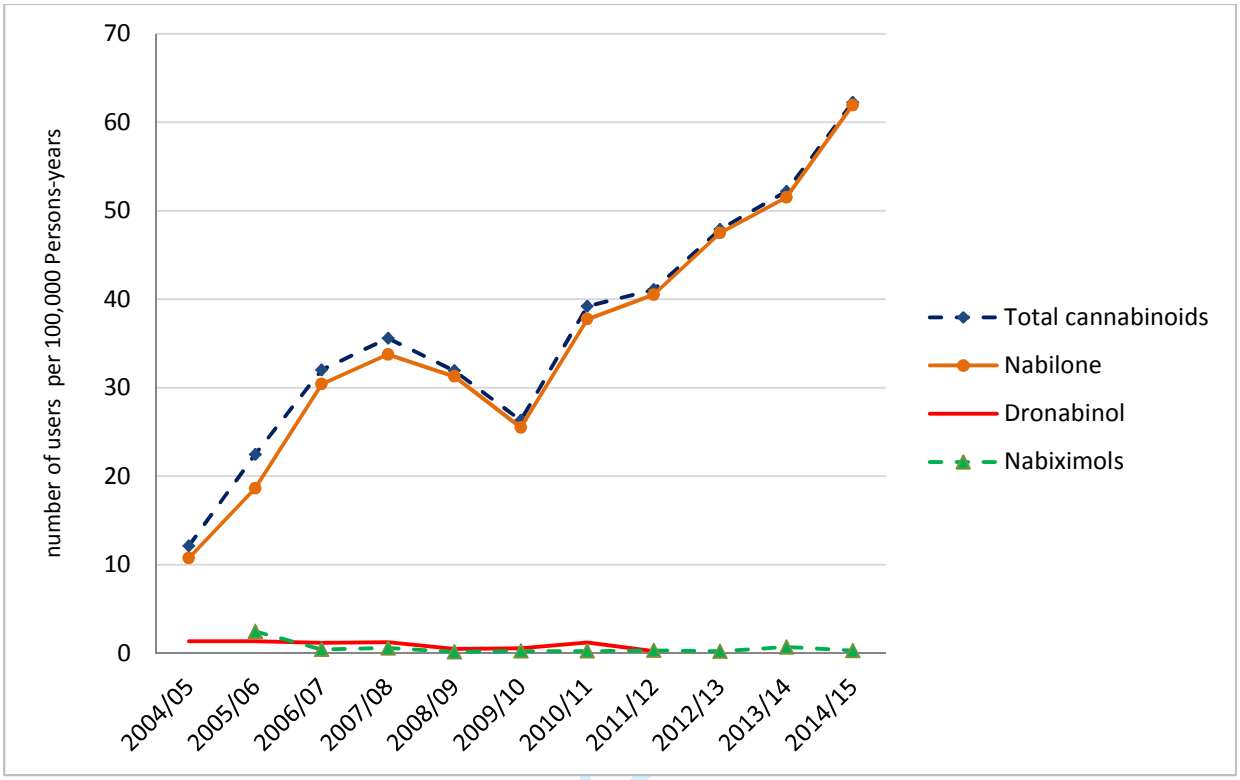

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Figure 2.A: Annual incidence rate of cannabinoid use by age group (2004/05-2014/15).

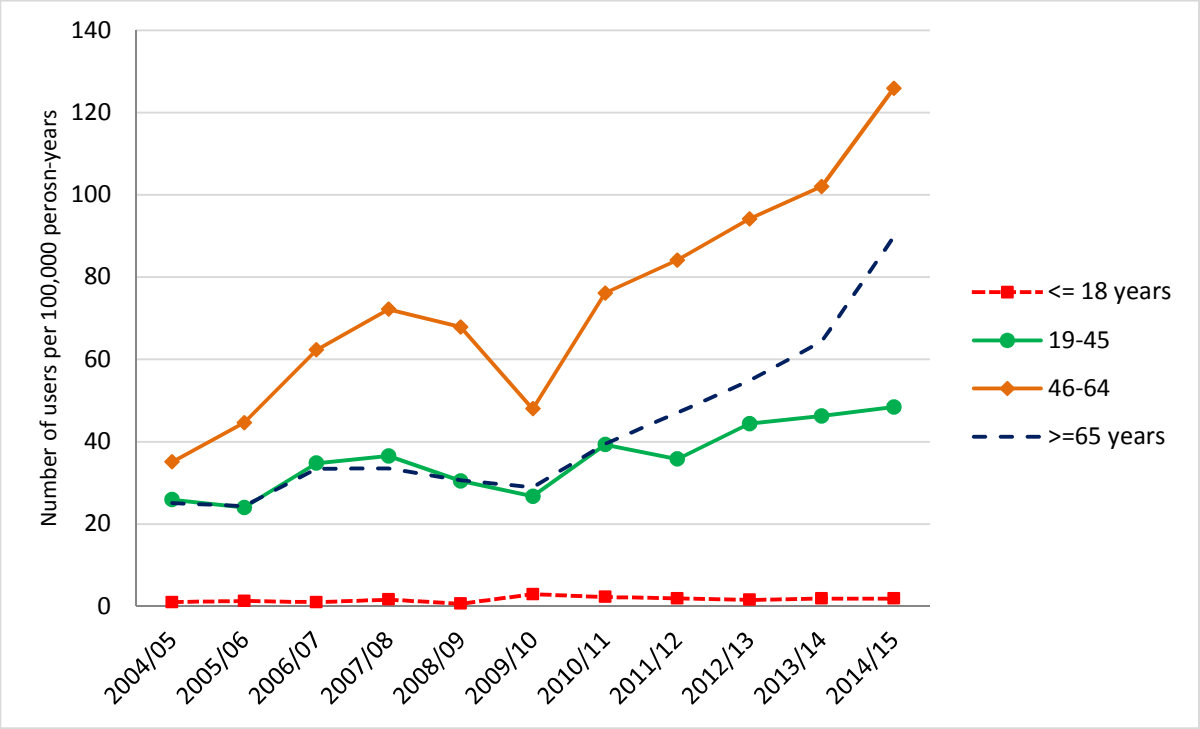

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Figure 2.B: Annual incidence rate of cannabinoid use by sex (2004/05-2014/15).

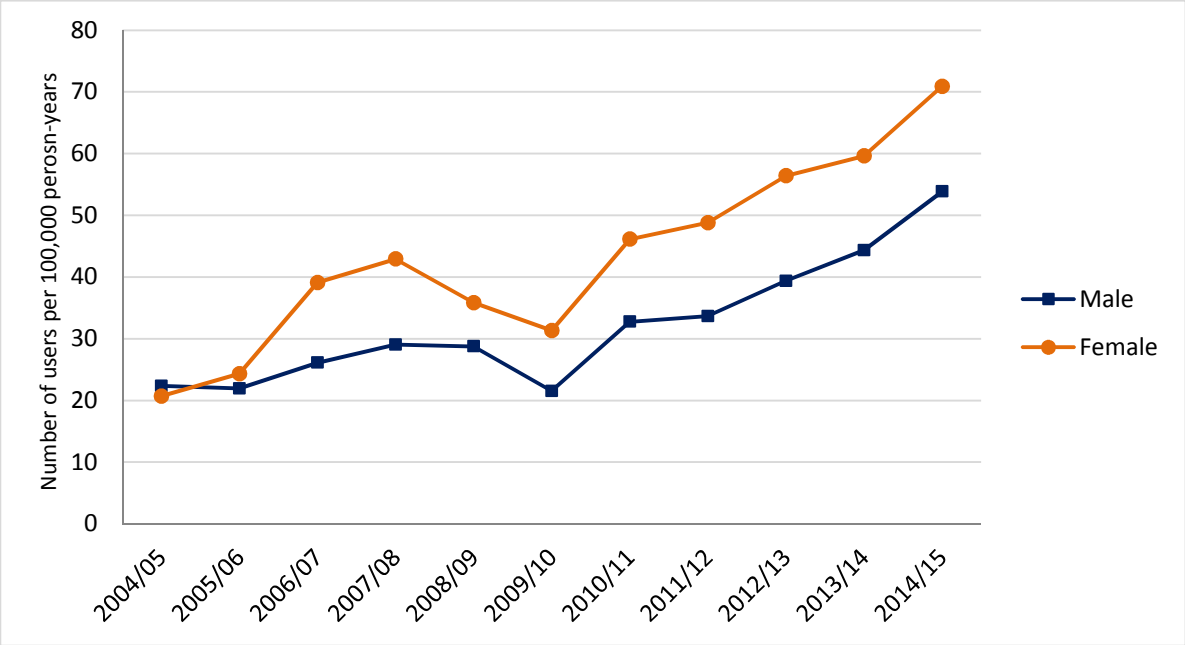

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Figure 2.C: Annual incidence rate of cannabinoid use by area of residence (2004/05-2014/15).

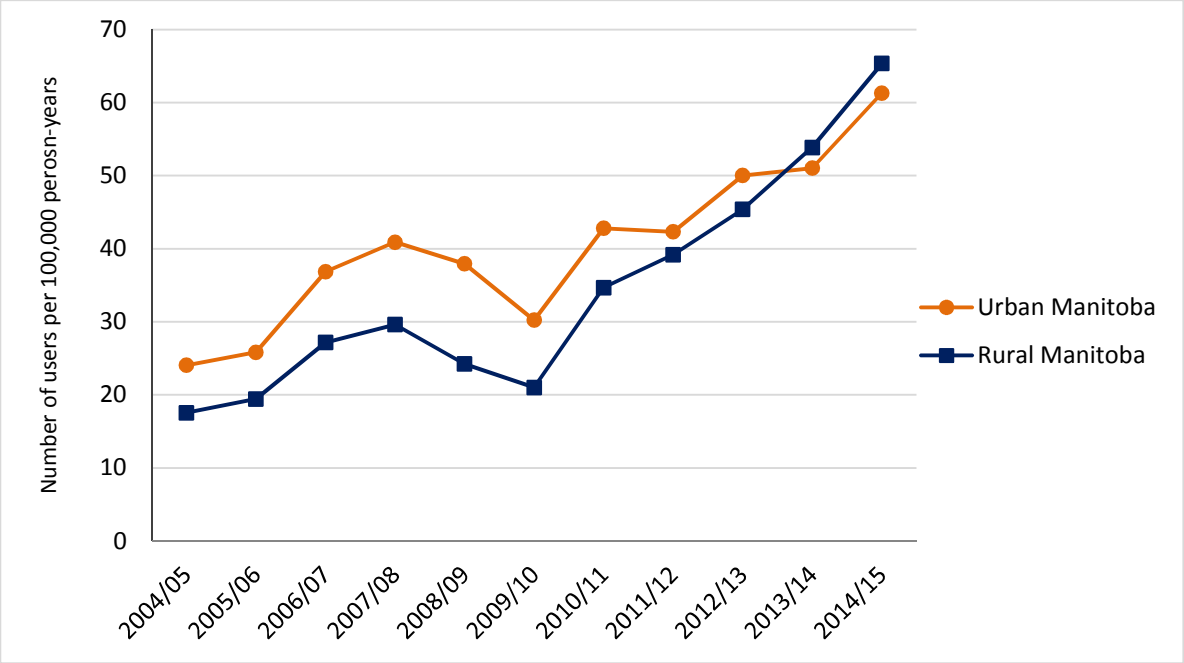

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Figure 3: Annual prevalence of cannabinoid users (2004-2015)

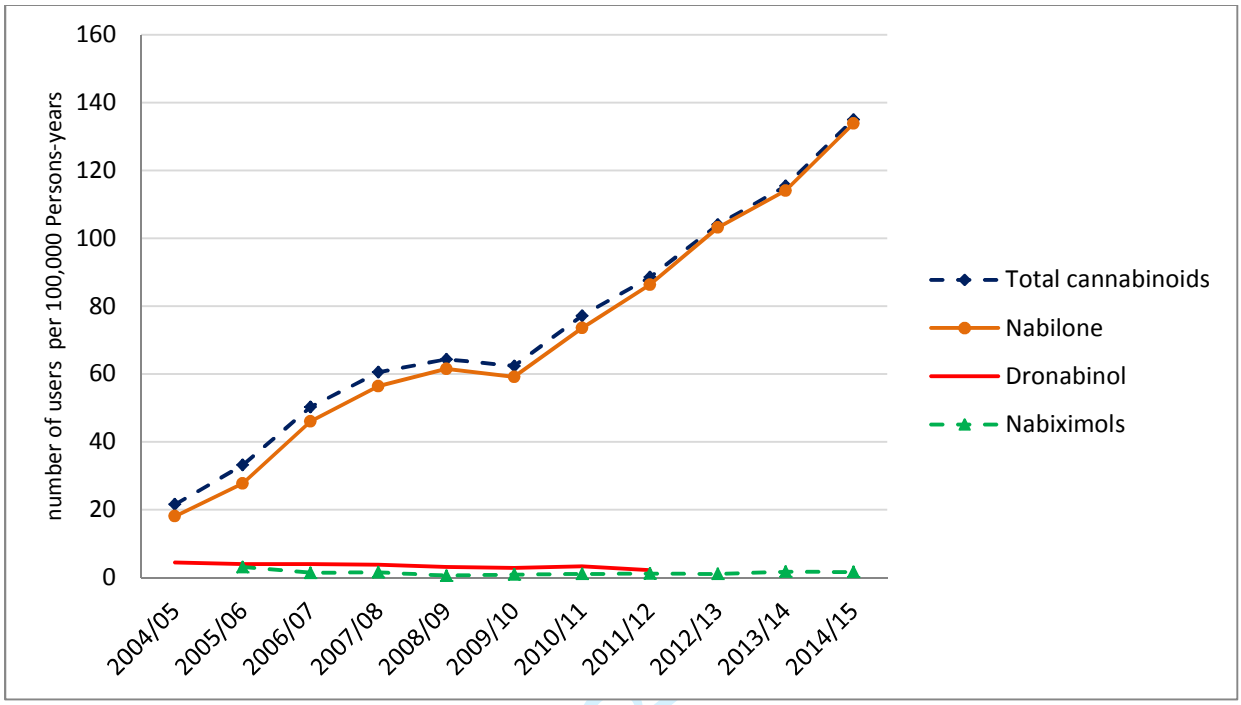

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Table1: Effect of time and socio-demographics on the prevalence and incidence of cannabinoid use in Manitoba, 2004/2005-2014/2015.

Variable	PREVALENCE			INCIDENCE		
	Relative rate	95% CI	P-value	Relative rate	95% CI	P-Value
Change in annual rate	1.15	1.14-1.16	<0.0001	1.09	1.08-1.10	<0.0001
Sex						
Female vs male	1.38	1.30-1.46	<0.0001	1.33	1.23-1.42	<0.0001
Age						
≤18 vs ≥65	0.03	0.02-0.04	<0.0001	0.04	0.03-0.06	<0.0001
19-45 vs ≥65	0.96	0.88-1.06	0.4647	0.82	0.74-0.91	0.0002
46-64 vs ≥65	2.28	2.09-2.49	<0.0001	1.70	1.53-1.89	<0.0001
Region						
Urban vs rural	1.17	1.10-1.24	<0.0001	1.11	1.04-1.19	0.0037
Socioeconomic status						
Low vs high	0.62	0.55-0.71	<0.0001	0.79	0.68-0.92	0.0025
Low-mid vs high	0.73	0.66-0.80	<0.0001	0.84	0.74-0.95	0.0057
Mid-high vs high	0.92	0.89-1.08	0.6712	1.06	0.94-1.19	0.3619

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Table 2: Medical conditions of incident cannabinoid users *

Condition	N	%
Chronic pain	2540	50.46
Fibromyalgia	1775	35.26
Mood/Anxiety	1116	22.17
Cancer	917	18.21
Osteoarthritis	662	12.35
Substance abuse	418	8.30
Multiple sclerosis	213	4.23
Glaucoma	169	3.35
Rheumatoid arthritis	155	3.07
HIV/AIDS	51	1.01
Schizophrenia	29	0.57
Epilepsy	27	0.53

*user can belong >1 group

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Supplementary Table 1: Algorithms for Identification of Medical Conditions among Prescription Cannabinoid Users. [27-32-]

Condition	Definition*	ICD 9	ICD 10
Epilepsy	1H and/or 3P**	345	G40,G41
Cancer	1H and/or 2P	140-172, 174-209	C00-C43, C45-C97
Schizophrenia	1H and/or 2P	295	F20-F25
HIV/AIDS	1H and/or 3P	042-043	B20-B24
Rheumatoid Arthritis	1H and/or 2P	714	M05,M06
Osteoarthritis	1H and/or 2P	715	M15,M16
Fibromyalgia	1H and/or 2P	729	M79
Multiple sclerosis	1H and/or 3P	340	G35
Substance abuse/misuse	1H and/or 1P	291,292,303,304,305	F10-F19,F55
Glaucoma	2 P	365	N/A
Mood/Anxiety disorders	A. 1H for (mood disorders), (stress and adjustment disorders), (mental and behavioral disorders), (emotional disorders).	A. (296.1,296.8), (300.4 309,311).	A. (F33, F36,F38), (F43),(F53),(F93).
	B. 1H for anxiety disorders, depressive disorder, mood disorders, obsessive-compulsive disorders dissociative disorders somatoform disorders + 1 Pres for antidepressant/mood stabilizer*	B. (300.0)	B. (F40, F41), (F32), (F34.1), (F42), (F44), (F45.0, F45.1).
	C. 3P for mood disorders, reaction to stress and adjustment disorders, depressive disorders.		
	D. 3P for anxiety disorders + 1 pres for antidepressant/ mod stabilizer.	C.(296),(309),(311)	
		D. 300	

* Within two years before the first cannabinoid prescription dispensation.
** physician claims separated by 30 days.

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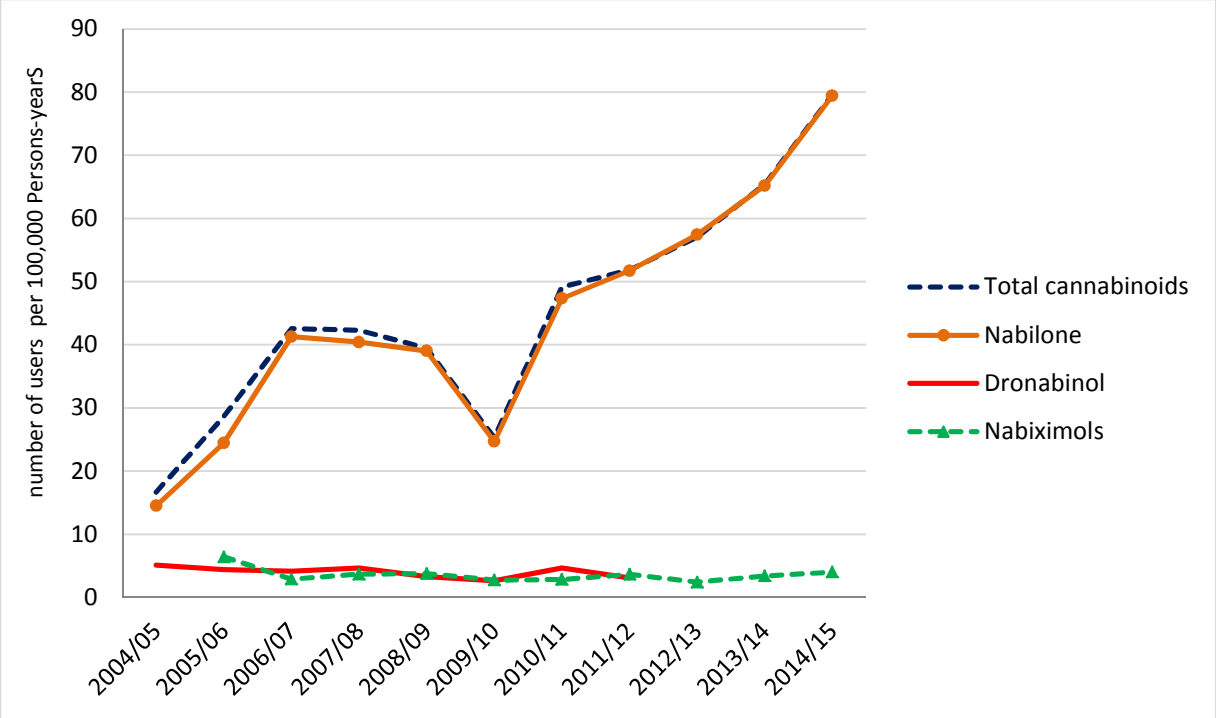
Supplementary figure 1: Annual incidence of cannabinoid users (2004/05-2014/15) standardized to the Canadian population (2016).



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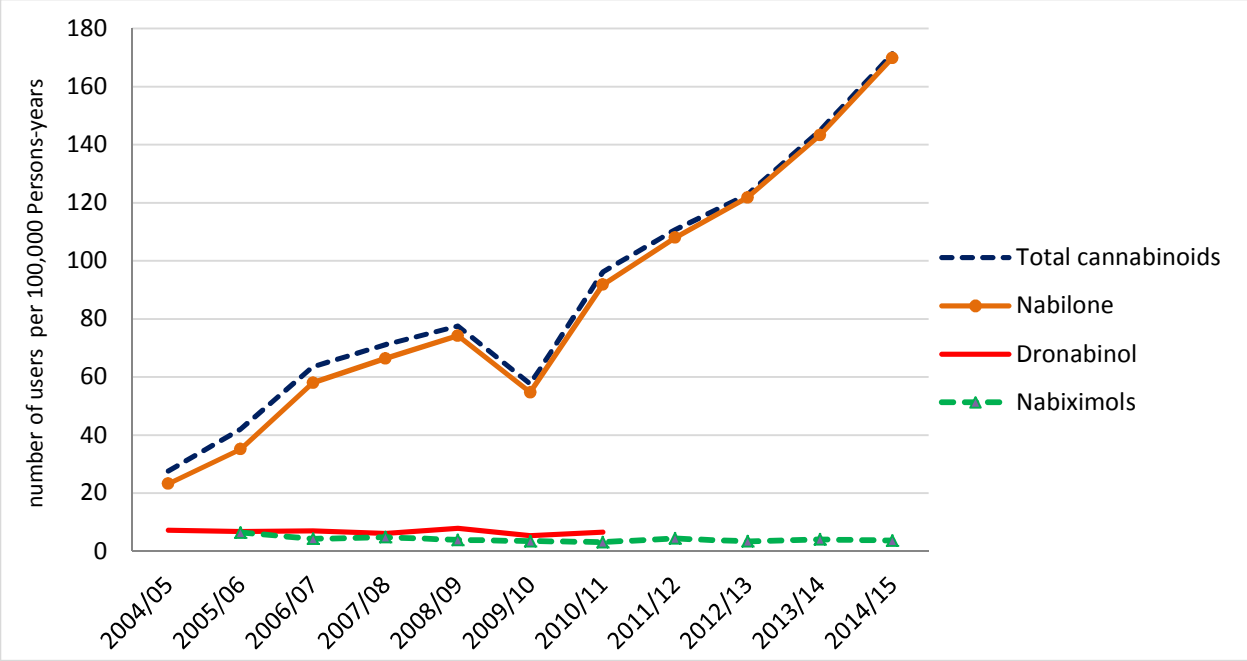
Supplementary figure 2: Annual prevalence of cannabinoid users (2004/05-2014/15) standardized to the Canadian population (2016).



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STROBE Statement—Checklist of items that should be included in reports of ***cohort studies***

	Item No	Recommendation	Submitted Manuscript
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract	Page 2-line 34
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found	Page 2
Introduction			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	Page 3-4 (rationale: lines 78-84)
Objectives	3	State specific objectives, including any prespecified hypotheses	Page 5 (lines:84-86)
Methods			
Study design	4	Present key elements of study design early in the paper	Page 4 : (lines 89-92)
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	Page 4-5 (lines 89-20)
Participants	6	(*a*) Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up	Page 5: (lines 107-108)
		(*b*) For matched studies, give matching criteria and number of exposed and unexposed	NA
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	Page 5-7 (lines 108-144)
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	*Page 5 (lines: 96-105)*
Bias	9	Describe any efforts to address potential sources of bias	Page 6 (lines 117-118) Page 12 (lines 260)
Study size	10	Explain how the study size was arrived at	Page 6 (lines 107-116)
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	Page 7 (lines:140-144)
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding	Page 6-7 (lines 132-146)
		(*b*) Describe any methods used to examine subgroups and interactions	Page 6 (lines 135-136)
		(*c*) Explain how missing data were addressed	NA
		(*d*) If applicable, explain how loss to follow-up was addressed	Page 7 (lines 139-140)
		(*e*) Describe any sensitivity analyses	NA
Results			

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Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed	Page 7 (lines:153-154)
		(b) Give reasons for non-participation at each stage	NA
		(c) Consider use of a flow diagram	NA
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	Page 8 (lines:160, 166-171) Page 9 (184-188) Table 1 Figure 2
		(b) Indicate number of participants with missing data for each variable of interest	NA
		(c) Summarise follow-up time (eg, average and total amount)	Mentioned throughout (11 years)
Outcome data	15*	Report numbers of outcome events or summary measures over time	Page 8 (lines: 161-165) Page 8 (lines: 175-181)
Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included	Page 8-9 (lines:159-188) Table 1
		(*b*) Report category boundaries when continuous variables were categorized	Table 1
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	NA
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	NA
Discussion			
Key results	18	Summarise key results with reference to study objectives	Page 9 (lines:197-199) Page 10 (lines:203-212)
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias	Page 11-12 (lines:243-254)
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	Page 10-11 throughout
Generalisability	21	Discuss the generalisability (external validity) of the study results	Page 12 (lines 259-261)
Other information			
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present	Page 12 (lines 263-264)

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	article is based

*Give information separately for exposed and unexposed groups.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at http://www.strobe-statement.org.

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